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Assessment of timing of hydrocortisone treatment and vasoactive inotrope scores in pediatric septic shock cases

Hydrocortisone treatment in septic shock

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Abstract

Aim: We aimed to investigate the relationship between the demographic characteristics of patients with septic shock who received hydrocortisone treatment, and the time of treatment initiation, doses, the relationship with different inotropes, and the relationship with vasoactive inotrope score.

Material and Methods: Our study included critically ill pediatric patients (n=41) while being monitored in the Pediatric Intensive Care Unit. Demographic data, primary diagnoses, systolic/diastolic/mean blood pressure levels, echocardiographic imaging findings (if any), hydrocortisone dosage, time of initiation after the first inotrope, total time of use, vasoactive inotrope scores and mortality status of patients were recorded in the data system and analyzed.

Results: Median (IQR) hydrocortisone infusion time was 36 (43) hours, time of initiation after the first inotrope median (IQR) was 24 (38) hours according to the calculation performed. There was no difference in initiation timing and infusion duration of hydrocortisone treatment between patients who received dopamine, dobutamine, or milrinone and those who did not (p>0.05). There was no correlation between the time after inotrope initiation and the infusion time of hydrocortisone (p=0.217, r2=-0.197). No significant difference was observed between mortality rates within the first 24 hours and at day 7, and the vasoactive inotrope score (p=0.345, p=0.954)

Discussion: Our study evaluated various parameters in patients who received hydrocortisone. If adrenal insufficiency is not previously diagnosed, it may take some time to consider the possibility of catecholamine resistance and decide to initiate hydrocortisone treatment. The definition of catecholamine-resistant septic shock is not clearly defined by a specific time.

Keywords

Pediatric Intensive Care Unit, Vasoactive Inotrop Score, Hydrocortisone, Catecholamine-Resistant Septic Shock

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Introduction

Sepsis and septic shock are a significant cause of mortality and morbidity in children [1]. Sepsis is a life-threatening condition resulting from a dysfunctional host response to infection. Death often occurs in the early period (first 48-72 hours) due to resistant shock and multiple organ failure. Therefore, early diagnosis and initiation of appropriate and effective treatment is vital [2]. The treatment for sepsis and septic shock typically involves fluid resuscitation, antibiotics, and inotropes/vasopressors. In cases where septic shock is resistant to vasopressors and fluids, corticosteroids are recommended [3]. The use of glucocorticoid therapy in patients with septic shock has improved since the 1990s [4]. The administration of glucocorticoids in patients with sepsis and septic shock is based on data suggesting that critical illness may lead to a state of absolute or relative adrenal insufficiency, which can contribute to shock. Normal serum cortisol levels range from 5 to 24 mcg/dL with considerable variability depending on the time of day. In critically ill patients, daily variability is lost, and serum cortisol levels increase, reaching levels as high as 40 to 50 mcg/dL. Other aspects of critical illness may significantly alter cortisol metabolism and function. These include decreased cortisol degradation, decreased binding of cortisol to cortisol-binding globulin and albumin, increased glucocorticoid receptor affinity for cortisol, and peripheral conversion of precursors to cortisol. Another proposed mechanism suggests that in critically ill patients, disruption of the hypothalamic-pituitary-adrenal axis, in combination with underlying diseases and various factors, leads to negative changes in cortisol levels and decreased efficacy [5-7].

The initiation of hydrocortisone treatment should be considered in these patients to improve their condition and to prevent mortality due to adrenal insufficiency. Glucocorticoids have long been used as an adjunctive agent in septic shock, and new studies are providing additional information about their mechanism of action [8]. In the current guidelines, this treatment is still presented in the category of low quality weak recommendation [1].

Vasoactive inotrope score is an effective indicator that reflects cardiovascular function by integrating and quantifying the dosage of vasoactive drugs used [9].

In our study, we aimed to investigate the relationship between the demographic characteristics of patients with septic shock who received hydrocortisone treatment, and the time of treatment initiation, doses, the relationship with different inotropes, and the relationship with vasoactive inotrope score.

Material and Methods

The study was designed as a retrospective and observational study. Our study included critically ill patients between the ages of 1 month and 18 years who were diagnosed with septic shock and received hydrocortisone treatment while being monitored in the Pediatric Intensive Care Unit at Health Sciences University Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital from January 2020 to June 2023. The diagnosis of septic shock was made based on the definition provided in the current Surviving Sepsis Campaign guidelines [1]. Patients were identified through the Hospital Information System by reviewing their diagnosis and medication information. Then, the patients' files and clinical follow-ups were analyzed. Demographic data, primary diagnoses, systolic/diastolic/average blood pressure levels, echocardiographic imaging findings (if any), hydrocortisone dose, time of initiation after the first inotrope, total time of use, presence of other inotropes and mortality status of patients (N=41) who received hydrocortisone infusion were determined and recorded in the data system. Mortality scores, specifically the Pediatric Risk of Mortality (PRISM IV) and Pediatric Logistic Organ Dysfunction (PELOD) scores, as well as VIS, were calculated based on the inotrope doses administered at the time of initiation of hydrocortisone treatment.

Vasoactive Inotrope Score

The Vasoactive Inotrope Score was calculated using the following formula: VIS = dopamine (μg/kg-min) + dobutamine (μg/kg-min) + 10 × milrinone (μg/kg-min) + 100 × epinephrine (μg/kg-min) + 100 × norepinephrine (μg/kg-min). The values at the time of initiation of hydrocortisone treatment were recorded in the data system [10].

Hydrocortisone protocol

The initial protocol for hydrocortisone treatment in our service starts with a 24-hour intravenous infusion of 50-100 mg/m2/day and is titrated to a maximum dose of 200 mg/m2/day [11, 12]. During this infusion, many hemodynamic parameters are dynamically monitored.

Statistical analysis

Statistical analysis of data was performed by SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). The distribution of the data was examined and mean standard deviation (SD) was given for normal distribution and median interquartile range (IQR) was given for non-normally distributed data. Independent T test or Mann Whitney U test was used to examine the differences between 2 groups in numerical data. Spearman correlation test was applied for correlation between numerical data.

Ethical Approval

This study was approved by the Ethics Committee of Izmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital Clinical Research (Date: 2023-08-20, No: 165).

Results

A total of 41 patients who were hospitalized in the pediatric intensive care unit and started hydrocortisone treatment because of catecholamine-resistant septic shock were identified. Demographic data, diagnosis, initial vital signs, dose and total usage duration of hydrocortisone, level of lactate, cortisol and mean (±SD) values of some variables are given in Table 1. It was determined that all patients received adrenaline and noradrenaline infusion, 25 (61%) patients received dopamine, 16 (39%) patients received dobutamine and 10 (24.4%) patients received milrinone infusion. There was no difference in initiation timing and infusion duration of hydrocortisone treatment between patients who received dopamine, dobutamine, or milrinone and those who did not. ($p>0.05$) (Table 2). Since all patients received adrenaline and noradrenaline infusion, these two inotropes were not included in the comparative analysis. There was no correlation between the time after inotrope initiation and the infusion duration of

hydrocortisone (p=0.217, r2=-0.197). There was no correlation between the maximum level of hydrocortisone used and ejection fraction measurements (p=0.126, r2=-0.260)

The mortality status of the patients at 24th hour and 7th day were compared with doses and the start time of hydrocortisone, vital signs, and ejection fraction. Hydrocortisone infusion duration was shorter in patients with mortality in the first 24 hours (p<0.05). When the presence of mortality on day 7 was analyzed, patients with mortality had a lower percentage of ejection fraction, but higher baseline diastolic blood pressure values (p<0.05) (Table 3).

No significant difference was observed between mortality rates within the first 24 hours and at day 7, and the vasoactive inotrope score (p=0.345, p=0.954). A weak positive correlation was found between the vasoactive inotrope score and the PELOD score (p=0.029, r2=0.340). Additionally, a moderate positive correlation was observed between the vasoactive inotrope score and the PRISM score (p=0.007, r2=0.418). Furthermore, there was no correlation found between the vasoactive inotrope score and the duration of hydrocortisone infusion, the time elapsed after the initial inotrope administration, the length of hospitalization, or the ejection fraction (p>0,05).

Table 1. Descriptive statistics of demographic and numerical variables

Variables	N (%)
Gender	
Female	18 (%43.9)
Male	23 (%56.1)
Primary diagnosis of Patients	
Cardiovascular Disease	1 (2.4)
Norological Disease	11 (26.8)
Renal Disease	2 (4.9)
Hematological Disease	8 (19.5)
Genetic Syndromes	2 (4.9)
Immunodeficiencies	1 (2.4)
Post-Operative Surgical Patients	1 (2.4)
Metabolic Diseases	11 (26.8)
Without Chronic Disease	4 (9.8)
Vital Signs and Lactate levels (Initial)	**Mean (±SD)**
Oxygen Saturation (%)	95.39 (3.31)
Heart Rate (per minute)	128.82 (28.23)
Systolic Blood Pressure (mmHg)	88.87 (17.38)
Diastolic Blood Pressure (mmHg)	55.02 (9.43)
Mean Arterial Pressure (mmHg)	61.73 (10.22)
Lactate levels (mmol/L)	9.06 (5.99)
Other Variables	**Median (IQR)**
Age (Months)	39 (73.5)
Dose of Hydrocortisone (mg/m2/day)	50 (50)
Infusion Duration of Hydrocortisone (hours)	36 (43)
Maximum Dose of Hydrocortisone (mg/m2/day)	100 (50)
Cortisol Levels (µg/dL)	3.73 (10.73)
Ejection Fraction (%)	62 (19.75)
Time After Inotrope Initiation (hours)	24 (38)

Table 2. Statistical analysis between hydrocortisone dose, infusion duration and time after the first inotrope start according to the type of inotrope used

Inotrop Types	Initial Dose of Hydrocortisone	Infusion Duration of Hydrocortisone	Time After Inotrope Initiation
	Median (IQR)	Median (IQR)	Median (IQR)
Dopamin			
Used (N=25)	50 (50)	24 (37.5)	24 (38)
Unused (N=16)	100 (50)	48 (55.75)	27 (55.25)
	p=0.036*	p=0.155	p=0.697
Dobutamin			
Used (N=16)	50 (50)	41 (67.5)	38 (39)
Unused (N=25)	50 (50)	24 (38.5)	24 (37)
	p=0.558	p=0.133	p=0.189
Milrinon			
Used (N=10)	75 (50)	27 (18.75)	48 (56.25)
Unused (N=31)	50 (50)	36 (68)	24 (36)
	p=0.473	p=0.419	p=0.068

Mann-Whitney U test *p<0.05

Table 3. Examination of the relationship between mortality and other variables

Variables	24th hour mortality			7th day mortality		
	Yes	No	P value	Yes	No	P value
Median (IQR)	(N=11)	(N=30)		(N=29)	(N=12)	
Initial Dose of Hydrocortisone	100 (50)	50 (50)	0.756	75 (50)	50 (50)	0.502
Infusion Duration of Hydrocortisone	22 (34.5)	36 (51.75)	0.013*	36 (34)	42 (74)	0.186
Oxygen Saturation	96.5 (5.5)	96 (5.5)	0.835	97 (4)	94 (4.5)	0.073
Systolic Blood Pressure	96.5(39.75)	85.5(19.75)	0.596	91 (25.75)	82.5 (19.25)	0.92
Mean Arterial Pressure	68 (13.25)	60 (16.75)	0.401	64 (18.75)	60 (9.5)	0.852
Lactate levels	13.5 (12.52)	7.79 (8.88)	0.393	9.1 (10.41)	6.4 (8.13)	0.229
Time After Inotrope Initiation (hours)	31 (32.5)	23 (41)	0.545	24 (38)	21 (42)	0.886
Maximum Dose of Hydrocortisone	100 (50)	100 (43.75)	0.238	100 (31.25)	90 (50)	0.429
Variables						
Mean (±SD)						
Diastolic Blood Pressure	59 (±7.98)	53.56(±9.62)	0,103	57.06 (8.89)	50.08 (9.18)	0.029**
Heart Rate (per minute)	130.9(27.74)	128 (28.84)	0.779	130.4 (26.46)	124.9(33.05)	0.575
Ejection Fraction (%)	61.87(15.02)	59.35(14.52)	0.67	56.6 (15.27)	68.4 (7.33)	0.004**

Hydrocortisone dose; mg/m2/day, Blood Pressure; mmHg, lactate;mmol/L, *Mann-Whitney U test p<0.05 **Student T-test

Discussion

Noradrenaline and adrenaline infusions were initiated in all patients who received hydrocortisone. Additional inotropic treatment was required based on the patient's central venous blood oxygen values, vital signs, and hemodynamic variables. Among these inotropes, it is believed that the high starting dose of hydrocortisone in patients who were not started on dopamine was due to physician preference in the hydrocortisone starting protocol. Additionally, there was no significant difference in the time elapsed between the initiation of the first inotrope and the administration of dopamine, milrinone, and dobutamine infusions in conjunction with adrenaline and noradrenaline infusions. It is important to consider the variability of inotropic and fluid responses in individual patients when evaluating the timing of hydrocortisone initiation. The doses of adrenaline and noradrenaline used in our study were not recorded. However, we did observe that hypotension persisted despite the administration of high doses.

Low ejection fraction during echocardiographic evaluation within the first week after the diagnosis of septic shock was significantly associated with mortality. Septic shock-induced acidosis and vascular compensation mechanisms may have a negative impact on cardiac reserve. The results can be explained as follows: The lower diastolic blood pressure of the patients who survived at the end of the first week does not necessarily indicate inadequate right heart filling volume and perfusion compared to the other group. Mean arterial pressures were maintained within the target range using multiple inotropes and fluid resuscitation in both groups. It is also worth noting that patients who died within the first 24 hours had shorter infusion times, as expected.

In our study, we would like to highlight the timing of the hydrocortisone infusion after the first inotrope. The lack of difference in mortality rates within the first 24 hours and at the end of the 7th day for this parameter suggests that septic shock and other underlying mechanisms may have a greater impact. Early diagnosis, timely initiation of broad-spectrum empirical antibiotic treatment, and aggressive inotropic and fluid therapy may have a greater impact on the mortality of patients with septic shock. This is already emphasized in current guidelines [1].

Prior to hydrocortisone treatment, it is important to consider patients' cortisol levels. Patients with septic shock exhibit a wide variation in total serum cortisol levels [7]. In a prospective study of 101 sepsis patients, it was reported that the most accurate predictor of adrenal insufficiency (measured by an overnight ACTH stimulation test) was a baseline random cortisol level of 10 microg/dL or less, or a cortisol change of less than 9 microg/dL [13]. Critically ill patients undergo a transition from inactive protein-bound cortisol to physiologically active free cortisol. It has been suggested that free cortisol more accurately reflects hypothalamohypophyseal axis activation in these patients [14]. When retrospectively analyzing our patients, we found median values of total cortisol levels in only 20 patients. Unfortunately, we were unable to measure free cortisol levels. It would have been useful to have control levels to determine the increase in cortisol levels, which were already expected to increase, compared to baseline levels. The analysis should separate the direct effect on the septic shock clinic from the effects of prior treatments, including hydrocortisone. Prospective controlled studies are needed, particularly in the pediatric age group. Additionally, studies have shown that the low dose ACTH stimulation test can increase basal cortisol levels in pediatric patients with septic shock [15].

The vasoactive inotrope score is a tool used to measure the degree of inotrope treatments frequently administered to critically ill patients. Studies have shown a correlation between high VIS and poor prognosis [16]. VIS is primarily utilized for postoperative survival analysis of patients who have undergone cardiac surgery. Gaies et al, found that those with higher VIS within 24 hours of cardiac surgery had an increased risk of death [17].

There are a limited number of reports on the relationship between VIS and the prognosis of septic shock in pediatric patients. Haque et al, categorized pediatric patients with septic shock into a VIS ≤ 20 group and a VIS > 20 group and found that VIS > 20 was an independent risk factor for death in children [18]. The absence of a significant difference between the vasoactive inotrope score and mortality in our study may be due to the small sample size and early mortality. The high median values of the vasoactive inotrope scores of our patients may have contributed to this outcome. Upon analysis, it was determined that the decision to administer hydrocortisone was made during the late period when the VIS scores of the patients were high, which aligns with the SSC guidelines. If adrenal insufficiency is not previously diagnosed, it may take some time to consider the possibility of catecholamine resistance and decide to initiate hydrocortisone treatment. The definition of catecholamine-resistant septic shock is not clearly defined by a specific time.

In this study, we evaluated cases where hydrocortisone infusion was used in combination with inotropes. Recent studies have shown that the early use of intravenous vitamin C, along with corticosteroids and thiamine, is effective in preventing progressive organ dysfunction, including acute kidney injury, and reducing mortality in cases of septic shock and severe sepsis. However, the use of this combination is still controversial [19, 20].

Conclusion

Our study evaluated various parameters in patients who received hydrocortisone. We concluded that the timing of hydrocortisone treatment did not significantly affect mortality rates of vasoactive inotropic scores in pediatric septic shock patients. One of the limitations of our study is that it was planned retrospectively. Additionally, we were not able to measure the patients' free cortisol levels. Studies on this topic in pediatric intensive care units in our country are limited. In the future, we recommend conducting controlled randomized prospective studies that evaluate free cortisol levels in conjunction with hydrocortisone treatment and the variability of inotrope requirement and mean arterial pressure.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some

of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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